Cortical plasticity: **Learning while you sleep?**

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Sleep has been suggested to facilitate memory consolidation or learning, but there has been little direct evidence of a link between synaptic plasticity and sleep. A recent study suggests a role for sleep in the plastic changes that the visual cortex undergoes in response to occlusion of one eye early in life.

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One of the big puzzles of life is why we (and most other vertebrates) sleep. We know that sleep deprivation, even after a short period, severely impairs physiological and mental functions, suggesting that sleep is needed to restore physical resources. But not all of sleep appears to be a time of rest. So-called 'paradoxical' sleep rather resembles wakefulness; heart rate, blood pressure and muscle tone increase, and darting 'rapid eye movements' are observed, giving rise to the term REM sleep. During this phase, it has been suggested, experiences made in the preceding waking period are replayed and their memory thus consolidated. Folklore has it that the knowledge of things rehearsed before going to bed will be acquired overnight, but how much scientific evidence is there for this?

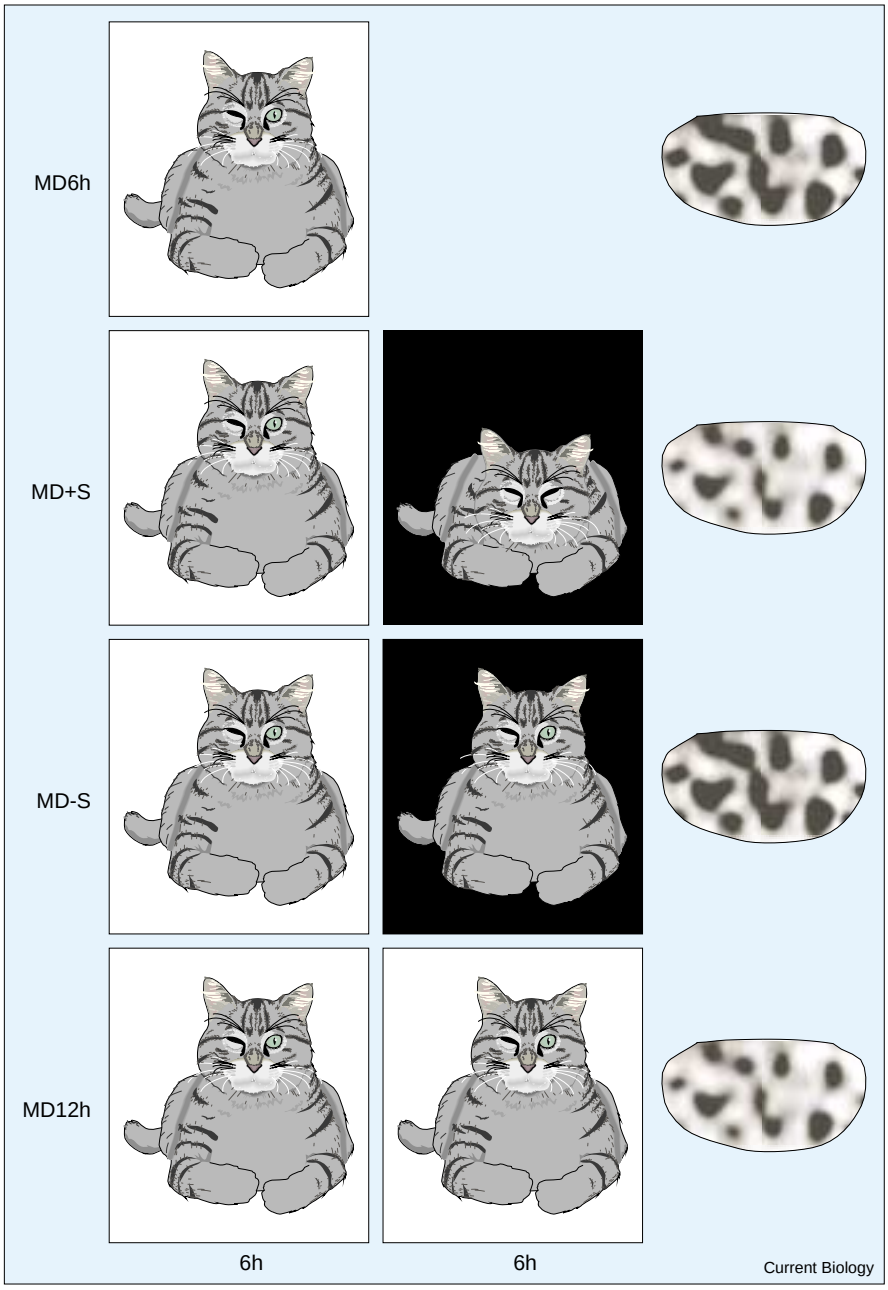
Direct evidence for a 'replay' of a waking experience during a substantial period of sleep comes from a recent study of zebra finches [1]. Neurons in the forebrain nucleus known as the robustus archistriatalis fire in characteristic bursts when the birds sing. For each note and syllable, this premotor activity has a characteristic firing pattern. When male finches were allowed to fall asleep, and their own song was played back to them, robustus archistriatalis neurons displayed an auditory response. For each syllable, the evoked firing pattern matched closely the bursts associated with it during vocalization. Similarly, the apparently spontaneous bursting activity of robustus archistriatalis neurons during sleep also resembles the waking (premotor) activity and can therefore be regarded as a replay of the latter. In mammals, a comparable replay of waking activity patterns during sleep was first reported for hippocampal 'place cells' in rats [2]. Cells that fired together during a spatial behavioural task also tended to fire together during a subsequent epoch of slow-wave sleep. Very recently, a replay of awake hippocampal ensemble activity has also been reported for REM sleep [3].

A number of recent studies have demonstrated effects of sleep on perceptual learning in humans. In a visual discrimination task, human subjects showed significant improvement when tested a day after initial training, and further improvement on the second and subsequent days. In contrast, there was no such improvement when subjects had been deprived of one night of sleep after training, but had been allowed to catch up on lost sleep during the next two nights [4]. These results show that sleep must occur within a certain time window after training to have a consolidating effect. While an earlier study [5] concluded that overnight improvement is blocked by selective deprivation of REM sleep, very recently the opposite was found when subjects were allowed either an 'early sleep' period (dominated by slow-wave, non-REM sleep) or 'late sleep' (dominated by REM sleep): the former promoted improved performance while the latter alone did not [6]. Taken together, these experiments provide good evidence for memory consolidation or 'learning' during sleep, but what about effects of sleep on synaptic plasticity, the neural phenomenon thought to underlie learning processes?

The classical paradigm for physiological studies of plasticity in the visual cortex is monocular deprivation. In the visual cortex of mammals with frontally positioned eyes, including man, most neurons are binocular, responding equally well to visual stimulation through either eye. The closure of one eye by lid-suture (or similarly, vision blurred by a dense cataract) during the so-called 'critical period' early in life results in a radical shift in 'ocular dominance' — the balance between the two eyes' control over the visual cortex — towards the non-deprived eye. Physiologically, a significant ocular dominance shift can be observed after a day or less of monocular deprivation [7].

In the past, it has been claimed that the outcome of monocular deprivation shows a consolidation effect, such that the magnitude of the ocular dominance shift is greater if it is assessed, not immediately after terminating monocular deprivation by re-opening the deprived eye, but instead after a certain time interval. Frank *et al.* [8] have now examined the role of sleep in this supposed consolidation process. They monocularly deprived 22 kittens of about a month of age (the height of the 'critical period') for just 6 hours. In one group of kittens, ocular dominance was assessed immediately afterwards (MD6h). In a second group (MD+S), the brief period of monocular deprivation was followed by 6 hours during which the kittens could sleep as much as they liked (in the dark). Another group (MD–S) instead had 6 hours of sleep deprivation, during which time the animals were kept awake in a dark room. A

Figure 1



Effect of sleep on the magnitude of the ocular dominance shift induced by monocular deprivation. The first two columns depict the rearing conditions of kittens employed by Frank *et al.* [8]. The right-most column schematically shows ocular dominance maps obtained from primary visual cortex under the various conditions. All kittens were monocularly deprived for 6 h, and one group was tested immediately afterwards (MD6h). A second group was allowed to sleep as much as they liked during the following 6 h (MD+S), while a third group was kept awake in the dark (MD–S). A fourth group was deprived for 12 h and then tested (MD12h). The ocular dominance maps obtained by intrinsic-signal imaging [9] display cortical regions dominated by the deprived eye in black, and those dominated by the non-deprived eye in white. The MD+S group shows a loss of territory dominated by the deprived eye well beyond that observed in the MD6h group, while the sleep-deprived group (MD–S) does not. In fact, the consolidation of the MD shift in the MD+S group amounts to about the same magnitude as is observed after 12 h of monocular deprivation (MD12h).

fourth group stayed in a light environment, such that they experienced a total of 12 hours monocular deprivation (MD12h). Sleep deprivation was ensured by gently moving the cage floor and by playing tape recordings of 'meowing' at the first signs of sleep onset. Sleep and wakefulness were assessed by electroencephalogram (EEG) and electromyogram (EMG) recordings, beginning 6 hours before the induction of monocular deprivation by eye-lid suture. The periods of monocular deprivation and of subsequent sleep deprivation had to be kept brief, as 12 hours of continuous wakefulness was considered the maximum young kittens could comfortably maintain.

Six hours of monocular deprivation caused a significant ocular dominance shift in the primary visual cortex towards the open eye, as was established by two independent methods [8]. By means of extracellular microelectrode recordings, the ocular dominance of neurons was determined at 300–400 sites in each of the four experimental groups. In a normal kitten, across both cortical hemispheres,

the left and the right eye dominate equal numbers of cells. The kittens with 6 hours of monocular deprivation displayed a relative ocular dominance shift of approximately 0.25 (with 1.0 signifying a complete shift towards the non-deprived eye). However, extracellular recordings from a necessarily limited number of sites always carry the risk of sampling bias.

A more objective assessment of ocular dominance is afforded by an imaging technique that allows visualization of activity in a large part of the primary visual cortex. This technique, optical imaging of intrinsic signals, relies on the difference in reflectance of incident red light between active and less active regions of the cortical surface. This difference is caused by changes in oxygenation of haemoglobin, as well by changes in light-scattering properties of active neural tissue [9]. Optical imaging confirmed the ocular dominance shift in the MD6h kittens, with the deprived eye dominating less than 50% of the cortical surface (Figure 1).

The central finding of the study by Frank *et al.* [8] is that, following a period of sleep (MD+S), kittens displayed a greater ocular dominance shift than immediately after monocular deprivation. In contrast, animals prevented from sleeping (MD–S) did not exhibit this 'consolidation' effect: if anything, the ocular dominance shift was slightly reduced in this group. Remarkably, the magnitude of the ocular dominance shift in the MD+S group was just as high as in the control group that experienced continuous monocular deprivation for 12 hours (MD12h). The results within each group were qualitatively and quantitatively similar, whether obtained by extracellular recording or by optical imaging (Figure 1).

As the respective roles of REM and slow-wave (non-REM) sleep in memory consolidation are still a matter of controversy (see above), Frank *et al.* [8] analysed the relationship between sleep patterns and the magnitude of the monocular deprivation effect in the MD+S and MD–S kittens. They found that there was a fairly linear relationship between the amount of non-REM sleep in the 6 hour period following the monocular deprivation and the ocular dominance shift index. Sleep deprivation reduced non-REM sleep to varying degrees (5–30% of the 6 h period), while REM sleep was virtually eliminated (<5%) in all the MD–S kittens. It was therefore not possible to test for a correlation between the amount of REM sleep and the ocular dominance shift.

On the other hand, the complete, selective deprivation of REM sleep has proved impossible, as attempts to produce such deprivation have been found to cause increasingly frequent interruptions of non-REM sleep and a reduction in the amounts and depth of non-REM sleep. Among the MD+S kittens, however, a weak negative correlation between the (high) amount of REM sleep and the ocular dominance shift index was observed. Interestingly, the only previous study to examine the role of sleep in visual cortical plasticity [10] found that, in kittens that were only slightly older, selective REM sleep deprivation over a one-week period strengthened the anatomical effects of monocular deprivation observed in the lateral geniculate nucleus. So while REM sleep appears to reduce visual cortical plasticity, Frank *et al.*'s data [8] suggest that non-REM sleep enhances or consolidates it.

Before accepting the obvious interpretation that sleep affects plastic changes in the visual cortex induced by a modification of the visual input, alternative explanations need to be considered. One possibility is that sleep deprivation induced the release of stress hormones, which in turn prevented a consolidation of the ocular dominance shift in the MD-S group. First, stress levels were kept low in this study by limiting sleep deprivation to a total 12 hours. Second, stress hormones such as corticosteroids and noradrenaline, though they can influence memory consolidation, are unlikely to account for the absence of ocular dominance shift consolidation in the study by Frank *et al.* [8]. Corticosterone has an effect on ocular dominance plasticity only at very high concentrations [11], and noradrenaline has been reported to restore, rather than inhibit, visual cortical plasticity [12].

A more serious concern about the interpretation of Frank *et al.*'s data [8] is the possibility that the effect of monocular deprivation on ocular dominance is enhanced during a subsequent period, regardless of whether the animal is awake or asleep. This phenomenon has also been termed 'consolidation' [13], and it may, for instance, be attributed to protein synthesis, which is triggered by changes in visual stimulation but will take a while to manifest itself in altered cortical responses.

A number of points diminish the likelihood of this explanation. First, such consolidation has been observed primarily for paradigms where the animals had no visual experience until given selective visual exposure for a brief period of time [13,14], but not in a case more similar to the study discussed here. On the contrary, Freeman and Olson [15] observed a reduction of the ocular dominance shift when short-term monocular deprivation was followed by two days in complete darkness before assessment of ocular dominance. Second, the sleep-deprived kittens did not show consolidation of the monocular deprivation effect. Finally, earlier studies reporting 'consolidation' of visual cortical response changes did not specify whether animals had been awake or asleep during the 'consolidation' period, and they are likely to have slept part of the time. On balance, it would therefore appear that sleep has at least a permissive role in visual cortical plasticity.

Answers to the following questions might permit more far-reaching conclusions. First, what is the magnitude of the ocular dominance shift when 6 hours of monocular deprivation are followed by 6 hours of general anaesthesia? This protocol should result in just a small ocular dominance shift if the larger shift in the MD+S group of kittens is caused specifically by sleep, rather than a non-specific period without conscious sensory experience or the absence of visual experience in the dark. Second, is there a critical time window after the sensory experience, within which sleep has to occur to have a consolidating effect? And perhaps most important, is there any long-term consolidation effect?

In Frank *et al.*'s study [8], the ocular dominance shift in the kittens with 6 hours of monocular deprivation and 6 hours of sleep was about the same as in the kittens with 12 hours of monocular deprivation, measured immediately afterwards. So one might argue that a bit more 'training' (in this case, visual experience) is just as good as some sleep, and sleep is therefore not necessary — even though it is sufficient — to promote consolidation. How would the two groups compare some time later? Frank *et al.* [8] have provided the first evidence for a role of sleep in a classical paradigm of cortical plasticity, but the search for the underlying mechanisms should keep researchers busy for some time yet.

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